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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/425,633 | Applicant(s) CHEE ET AL. | |
|---|---|---|---|
| | Examiner BJ Forman | Art Unit 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *22 October 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

**DETAILED ACTION**

***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-14 are indefinite because the claims are drawn to a method of determining the identification of nucleotide at a detection position but Claim 1, step a) does not provide the method or means for identifying a nucleotide at a detection position. The claims are further indefinite because Claim 1, step b) is a *non sequitur* to Claim 1, step a). It is suggested that Claim 1 be amended to recite positive, active and related method steps. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded. *Ex parte Erlich*, 3 USPQ2d 1011 at 6

b. Claims 1-14 are indefinite in step a) of Claim 1 for the in the recitation "said target sequence and a capture probe covalently attached to a microsphere" because it is unclear whether both the target sequence and the probe are attached to the microsphere. It is suggested that step a) of Claim 1 be amended to clarify e.g. "said target sequence and a capture probe wherein said capture probe is covalently attached...".

c. Claims 4 & 5 are indefinite because "readout position" in step i) of Claim 4 lacks proper antecedent basis in Claim 1. It is suggested that Claim 4, step i) be amended to properly depend from Claim 1 e.g. replace "readout" with "detection position".

d. Claims 4 & 5 are also indefinite because it is unclear whether the label is on the "unique nucleotide" and therefore it is unclear how label detection of Claim 4, step b) detects a "nucleotide at the detection position" and therefore the claims are further indefinite because Claim 4, step b) is a *non sequitur* to Claim 1, step a). It is suggested that Claim 4 be amended to recite positive, active and related method steps.

e. Claims 6-12 are indefinite in Claims 6 & 12 for the recitation of steps "a)" and "c)" without an intervening step "b)". It is suggested that the claim be amended to replace "c)" with "b)" or to clarify that steps "a)" and "c)" are further embodiments of steps "a)" and "c)" in Claim 1.

f. Claim 12 is indefinite in the recitation "said capture probe serves an extension primer" because a word appears to be missing and because "serves" is not standard scientific terminology. It is suggested that the claim be amended to clarify e.g. replace "serves" with "functions as".

g. Claims 13 & 14 are indefinite because it is unclear how label detection of Claim 13, step e) detects a "the presence or absence of said label as an indication of the formation of said cleavage structure" and the claims are further indefinite because Claim 13, step d) and step e) are *non sequitur* to one another. It is suggested that Claim 4 be amended to recite positive, active and related method steps.

h. Claims 13 & 14 are also indefinite in line 14 of Claim 13 for the recitation "contacting said hybridization complex with a cleavage enzyme that will cleave said detection sequence" because it is unclear whether the recitation is a method step or a characteristic of the enzyme. It is suggested that Claim 13 be amended to clarify e.g. "contacting said hybridization complex with a cleavage enzyme and cleaving said detection sequence".

i. Claims 13 & 14 are indefinite in the last line of Claim 13 because "the base" lacks proper antecedent basis in Claim 1. It is suggested that Claim 13 be amended to recite "the nucleotide".

j. Claims 15 & 16 are indefinite in Claim 15, step c) for the recitation "providing a ligation enzyme that will ligate said first and said second ligation probes to form a ligated probe" because it is unclear whether the recitation is a method step of ligation or a recitation of the enzyme characteristics. It is suggested that the claim be amended to clarify e.g. "ligating said first and second ligation probes with a ligation enzyme to form a ligated probe".

k. Claims 15 & 16 are indefinite in Claim 15, step d) because it is unclear how the assay complex is formed between the ligated probe, capture probe and label. It is suggested that Claim 15 be amended to clarify e.g. d) forming an assay complex by hybridizing said ligated probe, a capture probe covalently attached to a microsphere on a surface of a substrate and at least one label".

l. Claims 15 & 16 are indefinite in Claim 15, step d) because "ligated probe" lacks proper antecedent basis in step b) which recited "ligation structure". It is suggested that Claim 15, step d) be amended to replace "ligated probe" with "ligation structure".

m. Claims 15 & 16 are also indefinite in Claim 15 because it is unclear how detecting the label recited in step d) detects the formation of "said ligation structure" recited in step e) and therefore because steps d) and e) *non sequitur* to one another. It is suggested that Claim 15 be amended to recite positive, active and related method steps.

n. Claim 15 is indefinite in step f) because "the base" lacks proper antecedent basis in the claim preamble. It is suggested that the claim be amended to replace "the base" and with "the nucleotide".

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-12 & 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524, filed 9August 1996) in view of Walt et al. (U.S. Patent No. 6,023,540, filed 14 March 1997).

Regarding Claim 1, Nikiforov et al. teach a method of determining the identification of a nucleotide at a detection position in a target sequence comprising: providing a hybridization complex comprising said target sequence and a capture probe (which is the first oligonucleotide) determining the nucleotide at said detection position (Column 5, line 62-Column 6, line 5 and 41-44) and wherein said capture probe is covalently attached to a microsphere i.e. bead (Column 11, lines 6-10). Nikiforov et al. do not teach the microsphere on a surface. However, microspheres on a surface were known and routinely practiced in the art as taught by Walt et al. who teach a similar method for providing a hybridization complex comprising said target sequence and a capture probe covalently attached to microspheres on a surface of a substrate (Column lines 4-14) and they teach the advantages of the microspheres on a surface i.e. the method provides for the individual identification of thousands or more different functionalities (Abstract). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Nikiforov et al. with the teachings of Walt et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the microspheres of Nikiforov et al. and to position the microspheres on the surface of a substrate as taught by Walt et al. for the expected benefit of individually detecting thousands detection positions.

Regarding Claim 2, Nikiforov et al. teach the method of Claim 1 wherein said hybridization complex comprises said capture probe (which is the first oligonucleotide) and adapter probe (which is the second oligonucleotide) and said target probe (Column 6, lines 6-9).

Regarding Claim 3, Walt et al. teach said hybridization complex comprising said target sequence and a capture probe covalently attached to a microsphere on a surface of a substrate wherein said substrate is a fiber optic bundle (Column 4, lines 4-8).

Regarding Claim 4, Nikiforov et al. teach the method of Claim 1 wherein said determining comprises: contacting said microsphere with a detection probe (the second oligonucleotide) wherein the detection probe comprises a detectable label wherein following extension, the probe comprises a unique nucleotide at the detection position and detecting the signal from said detectable label to identify the nucleotide at the detection position (Column 7, lines 12-20). Nikiforov et al. do not teach the method comprising a plurality of detection probes. However, determining the identification of a nucleotide with a plurality of probes was known and routinely practiced in the art at the time the claimed invention was made. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Nikiforov et al. with routinely practiced procedures to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the nucleotide detection of Nikiforov et al. wherein the detection comprises a plurality of probes for the obvious benefit of detecting any and all possible nucleotides at the detection position of the target sequence.

Regarding Claim 5, Nikiforov et al. teach the method of Claim 4 wherein the detectable labels are fluorophores (Column 7, line 1).

Regarding Claim 6, Nikiforov et al. teach the method of Claim 1 wherein said target sequence comprises a first target domain directly 5' adjacent to said detection position wherein said hybridization complex comprises said target sequence, said capture probe and an extension primer hybridized to said first target domain of said target sequence and said determining comprises: contacting said microsphere with a polymerase enzyme, a plurality of NTPs comprising a covalently attached detectable label under conditions whereby if one of said NTPs base pairs with the base at said detection position, said extension primer is extended by

said enzyme to incorporate said label and identifying the base at said detection position (Column 7, lines 3-11).

Regarding Claim 7, Nikiforov et al. teach the method of Claim 6 wherein said label is a fluorophore (Column 7, line 1).

Regarding Claim 8, Nikiforov et al. teach the method of Claim 6 wherein said label is a fluorophore (Column 7, line 1) but they do not teach each NTP comprises a unique fluorophore. However, primer extension in the presence of NTPs each having a unique fluorophore was known and routinely practiced in the art at the time the claimed invention was made. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Nikiforov et al. with routinely practiced procedures to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the fluorescently detectable NTPs of Nikiforov et al. with each NTP comprising a unique fluorophore for the obvious benefit of determining the NTP by detecting the unique fluorophore and the known benefit of combining all 4 NTPs in one assay and thereby economizing time, labor and costs.

Regarding Claims 9-11, Nikiforov et al. teach the method of Claim 6 wherein said label is a hapten (Column 6, lines 65-67) and they teach the hapten is biotin (Column 17, lines 47-52) but they do not teach the hapten comprises, imine-biotin (Claim 10) and a functional group for addition of a fluorophore (Claim 12). However, haptens comprising imine-biotin and a functional group for addition of a fluorophore were known and routinely practiced in the art at the time the claimed invention was made. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Nikiforov et al. with routinely practiced procedures to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the haptens of Nikiforov et al. with routinely practiced haptens based on available reagents and equipment and for the benefit of convenience and economy.

Regarding Claim12, Nikiforov et al. teach the method of Claim 1 wherein said target sequence comprises a first target domain directly 5' adjacent to said detection position wherein said capture probe serves as an extension primer and is hybridized to said first target domain of said target sequence and said determining comprises: contacting said microsphere with a polymerase enzyme, a plurality of NTPs comprising a covalently attached detectable label under conditions whereby if one of said NTPs base pairs with the base at said detection position, said extension primer is extended by said enzyme to incorporate said label and identifying the base at said detection position (Column 6, lines 56-64).

Regarding Claim 15, Nikiforov et al. teach a method of identification of a nucleotide at a detection position in a target sequence comprising a first target domain comprising said detection position and a second target domain adjacent to said detection position said method comprising: hybridizing a first ligation probe to said first target domain, hybridizing a second ligation probe to said second target domain and extending one base, wherein if said second ligation probe comprises a base that is perfectly complementary to said detection position a ligation structure is formed, providing a ligation enzyme that will ligate said first and said second ligation probes to form a ligated probe, forming an assay complex with said ligated probe, a capture probe covalently attached to a substrate and at least one label, detecting the presence or absence of said label as an indication of the formation of said ligation structure and identifying the base at said detection position (Column 8, lines 3-14) wherein said capture probe is attached to a microsphere (Column 11, lines 6-10). Nikiforov et al. do not teach the microsphere on a surface. However, microspheres on a surface were known and routinely practiced in the art as taught by Walt et al. who teach a similar method for providing a hybridization complex comprising said target sequence and a capture probe covalently attached to microspheres on a surface of a substrate (Column lines 4-14) and they teach the advantages of the microspheres on a surface i.e. the method provides for the individual identification of thousands or more different functionalities (Abstract). It would have been

*prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Nikiforov et al. with the teachings of Walt et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the microspheres of Nikiforov et al. and to position the microspheres on the surface of a substrate as taught by Walt et al. for the expected benefit of individually detecting thousands detection positions.

Regarding Claim 16, Nikiforov et al. teach the method of Claim 15 wherein said label is a fluorophore (Column 7, line 1).

5. Claims 13 & 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524, filed 9August 1996) in view of Walt et al. (U.S. Patent No. 6,023,540, filed 14 March 1997) as applied to claim 1 above, and further in view of Lyamichev et al. (Nature Biotechnology, March 1999, 17: 292-296).

Regarding Claim 13, Nikiforov et al. teach the method of Claim 1 wherein said target sequence comprises 5' to 3' a first target domain and a second target domain wherein said hybridization complex comprises: a first probe hybridized to said first target domain and a second probe hybridized to said second target domain wherein said second probe comprises: a detection sequence and a detectable label, forming an assay complex with said detection sequence, a capture probe covalently attached to a microsphere and at least one label, detecting the presence or absence of said label as an indication of the formation of said structure and identifying the base at said detection position (Column lines 4-14). Nikiforov et al. do not teach the microsphere on a surface. However, microspheres on a surface were known and routinely practiced in the art as taught by Walt et al. (Column lines 4-14) and discussed above. Additionally, Nikiforov et al. do not teach said first target domain comprises an overlap domain comprising at least a nucleotide in the detection position wherein if said

second probe comprises a base that is perfectly complementary to said detection position a cleavage structure is formed. However, Lyamichev et al. teach a similar method for determining the identification of a nucleotide at a detection position in a target sequence comprising: a target sequence comprising 5' to 3' a first target domain comprising an overlap domain and a second target domain contiguous with said detection position wherein a first and second probe hybridize respectively to said first and second domain wherein if said second probe comprises a base that is perfectly complementary to said detection position a cleavage structure is formed, contacting said cleavage structure with a cleavage enzyme, forming an assay complex with said detection sequence to thereby detect said cleavage structure and identify the base at said detection position (page 292, right column, paragraphs 1 & 2 and Fig. 2). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Nikiforov et al. with the teachings of Walt et al. and Lyamichev et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the nucleotide detection of Nikiforov et al. with the hybridization and cleavage of Lyamichev et al. for the expected benefits of quantitative detection of a single nucleotide without amplification and the elimination of the primer extension reactions as taught by Lyamichev et al. (page 292, right column second paragraph). The skilled practitioner would have been further motivated to modify the microspheres of Nikiforov et al. with the microspheres on the surface of a substrate for the expected benefit of individually detecting thousands detection positions.

Regarding Claim 14, Nikiforov et al. teach said label is a fluorophore (Column 7, line 1).

**Conclusion**

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
August 24, 2000

S. Horner